

## Leonard Colebrook's Use of Sulfonamides as a Treatment for Puerperal Fever (1935-1937) <sup>[1]</sup>

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Between 1935 and 1937, Leonard Colebrook showed that sulfonamides, a class of antibacterial drugs, worked as an effective treatment for puerperal fever. Puerperal fever is a bacterial infection that can occur in the [uterus](#) <sup>[2]</sup> of women after giving birth. At the time of Colebrook's study, puerperal fever remained a common disease due to both the lack of hygienic practices in hospitals and a treatment for the disease. After successfully using Prontosil, a sulfanilamide, to cure a patient who was going to die from puerperal fever, Colebrook began experiments with the drug. He successfully treated patients with puerperal fever with sulfonamides, specifically Prontosil and sulfanilamide. Colebrook conducted the experiment from 1935 to 1936 primarily at the Queen Charlotte's Hospital in London, England. After Colebrook's success using antibacterial drugs in treating puerperal fever, use of antibacterial drugs became widespread in developed countries and, by the 1950s, it had made maternal deaths rare in those countries.

From 1900 to 1935, puerperal fever was responsible for approximately 1 in 100 maternal deaths in developed countries. That maternal death rate was lower than prior centuries, when puerperal fever accounted for approximately forty-five percent of maternal deaths. The decrease in maternal deaths in developed countries during the 1900s was largely due to better environmental conditions and obstetrical care. Additionally, some hospitals used preventative measures for puerperal fever like the use of hand washing. In the 1840s, Semmelweis studied the disease and successfully implemented a set of preventative measures at the Vienna General Hospital in Vienna, Austria. Semmelweis concluded that doctors were infecting women with puerperal fever when they transferred infectious material to the patients via their unclean hands. Semmelweis found that puerperal fever could be prevented with antiseptic procedures such as proper hand washing with chlorinated solutions. Nevertheless, during the nineteenth and early twentieth centuries, the medical community rejected Semmelweis's conclusions, and puerperal fever was still common in the 1920s, when Colebrook began his research.

In 1928, the [Medical Research Council](#) <sup>[3]</sup>, a government agency that funds medical research in the United Kingdom, appointed Colebrook as the head of a research team created to find a cure for puerperal fever. By 1934, Colebrook, with the help of his research team, had found that infection with Group A hemolytic streptococci bacteria caused puerperal fever. Group A streptococci bacteria are a type of bacteria that cause many bacterial illnesses in [humans](#) <sup>[4]</sup>. At the same time, researchers in Germany discovered sulfonamide, the basis for several groups of antibacterial drugs. In his experiments, Colebrook tested two groups of drugs based on sulfonamide: Prontosil and sulfanilamide.

In 1935, Colebrook began a study in which he treated puerperal fever in mice using Prontosil. Prontosil was the first sulfonamide drug discovered, and in the 1930s a research team at

Bayer Laboratories in Frankfurt, Germany, used it against streptococcus bacteria. Colebrook performed his study with one of his colleagues, Méave Kenny. They infected three groups of mice with lethal doses of puerperal fever. One group of mice served as a control and did not receive any treatment. They injected the second group of mice with 7.5 mg of Prontosil an hour and a half after inoculating puerperal fever, and they gave the mice additional doses of Prontosil five hours later and then every day for six days. Next, they gave the third group of mice double the amount of Prontosil via a stomach tube one and a half hours after inoculation and then again, the next day. They repeated the experiment twice, once with the time intervals increased, and another time with the dosage of Prontosil increased. Colebrook and Kenny found that sixty-four percent of the mice treated with Prontosil survived. They also found that treating the mice with Prontosil was better than no treatment, as Prontosil prevented infections from spreading to mice's stomach and increased the mice's chances of survival. When they increased the dosage of Prontosil, seventy percent of the mice survived, but there was a deposit of unused Prontosil at the injection site.

After conducting trials with Prontosil, Colebrook and Kenny conducted a trial with sulfanilamide, another drug in the class of sulfonamides. Sulfanilamide was slightly different than Prontosil in structure. They repeated the procedures with the mice. Only one of the mice treated with sulfanilamide died. Following the success of treating puerperal fever with sulfonamides in mice, Colebrook began testing the use of the two antibacterial sulfonamide drugs, sulfanilamide and Prontosil, in human patients.

In 1936, Colebrook began testing sulfanilamide as an antibacterial treatment of puerperal fever with his first assistant, Anthony W. Purdie. Colebrook asked three questions about the use of sulfanilamide. He asked whether or not sulfanilamide was effective against three groups of bacteria: multiple types of Group A hemolytic streptococci, other groups of hemolytic streptococci, and other bacteria besides hemolytic streptococci. The two researchers tested sulfanilamide in 106 women with puerperal fever. One hundred women had puerperal fever caused by infection with hemolytic streptococci. Ninety-two of the hundred women with puerperal fever were infected with Group A hemolytic streptococci and eight other women were infected with a different group of hemolytic bacteria. Additionally, three women had puerperal fever caused by anaerobic streptococci, which are bacteria that do not need air to grow. The remaining three women Colebrook and Purdie treated were infected with staphylococci bacteria, bacteria that cause infection by producing toxins.

Colebrook treated all 106 women who had puerperal fever with the antibiotic sulfanilamide. Colebrook based the dosage of sulfanilamide each woman received on the severity of the puerperal fever. Severe cases of puerperal fever exhibited distinct symptoms like high body temperature and low blood pressure. In women with severe cases of puerperal fever, Colebrook gave them eight to twelve grams of sulfanilamide per day and gave women with less severe cases three to six grams per day. On average, the women Colebrook treated stayed at the hospital for twenty days.

Colebrook compared the results of sulfanilamide as a treatment for puerperal fever to Prontosil as a treatment for puerperal fever. He found that the use of sulfanilamide decreased high fevers, one of the major symptoms of puerperal fever, and that sulfanilamide caused the blood of patients to greatly inhibit hemolytic streptococci. However, in comparison to Prontosil, Colebrook found that sulfanilamide did not act as fast in patients. Sulfanilamide caused high fevers to drop but not as drastically as Prontosil, and using sulfanilamide did not always eliminate the fever completely. Colebrook also compared the mortality rate of patients with

puerperal fever from 1932 to 1937 at Queen Charlotte's Hospital to determine if the use of Prontosil had changed the mortality rate. From 1932 to 1935, mortality rates of patients with puerperal fever gradually had decreased from ninety-three percent to sixty-seven percent. Colebrook asserted that the gradual decrease was due to his implementation of antibacterial hand washing procedures. In 1936 and 1937, the mortality rate for patients with puerperal fever was twenty-seven percent.

Colebrook found that sulfanilamide was an effective treatment for puerperal fever. In the 106 pregnant women treated with sulfanilamide, only eight died. Of those eight women, three deaths were directly attributed to puerperal fever. Colebrook found that sulfanilamide was effective against different serological types of Group A hemolytic streptococci. He also concluded that there were not enough pregnant women infected with the other groups of hemolytic streptococci to determine whether or not sulfanilamide was an effective treatment against multiple groups of streptococci bacteria. He made the same conclusion for the use of sulfanilamide in treatment of other bacteria besides hemolytic streptococci.

Colebrook's experiment with sulfanilamide, along with his experiment using Prontosil, demonstrated the clinical value of using sulfonamide drugs to puerperal fever. Following Colebrook's success with those antibacterial drugs in the treatment of puerperal fever, researchers conducted many experiments in Europe with the drug as a treatment for other various bacterial diseases. Because the research supported Colebrook's findings, the medical community began using drugs like sulfanilamide to treat bacterial infections. Additionally, in 1936 Franklin D. Roosevelt Jr., the son of the US President Franklin D. Roosevelt, had a throat infection that was treated with Prontosil, sulfamidochrysoidine. His treatment was highly publicized and resulted in the widespread use of antibacterial drugs. Prontosil was the first commercially available antibacterial sulfonamide drug.

Colebrook's experiment with sulfanilamide established it as an effective treatment for puerperal fever. Prior to his work on puerperal fever, there was no treatment for the disease and there were only preventative measures. With the introduction of antibacterial drugs, puerperal fever, a disease that caused the death of many women, has become rare in developed countries.

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